REMARKS

Request for Withdrawal of Finality

The outstanding Office Action was made final. MPEP § 706.07(a) specifies the conditions under which the finality of a second or subsequent Office Action is proper, providing that:

> "Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement…."

Applicants respectfully submit that the finality of the outstanding Office Action is improper under MPEP § 706.07(a) because the Examiner introduces new grounds of rejection that are neither necessitated by Applicants' amendments nor based on an information disclosure statement. As such, the finality is premature and thus withdrawal of the finality pursuant to MPEP § 706.07(d) is respectfully requested.

The Examiner stated that "[t]he claim amendments require for the first time that the composition contain a population comprising keratinocyte basal cells, melanocytes, and fibroblasts; previously, all that was required was that the cells be viable. The new rejections were necessitated by the amendments to the independent claims." Office Action at page 6, emphasis added. Applicants respectfully disagree. The recitation of keratinocyte basal cells, melanocytes, and fibroblasts was not presented for the first time in the Amendment and Response filed April 29, 2010. In contrast, the recitation was presented in the preceding Amendment and Response filed October 19, 2009. Specifically, the relevant prosecution history is as follows:

1. In the Amendment and Response filed October 19, 2009, the independent claims recite "said composition has a ratio of keratinocyte basal cells, melanocytes, and fibroblasts that is comparable to…."
2. In the non-final Office Action dated December 29, 2009, the Examiner requested clarification of "ratio" (see page 4).

3. In the Amendment and Response filed April 29, 2010, Applicants amended the claims to remove "ratio" and to recite "said composition has a cell population comprising keratinocyte basal cells, melanocytes, and fibroblasts."
4. In the final Office Action dated July 9, 2010, the Examiner alleges that the claims "require for the first time" keratinocyte basal cells, melanocytes, and fibroblasts (see page 6).

From the above prosecution history, it is clear that the recitation of keratinocyte basal cells, melanocytes, and fibroblasts was previously presented for examination (i.e., in the preceding Office Action dated December 29, 2009). Thus, the recitation cannot be reasonably said to be presented for the first time in the outstanding Office Action.

Furthermore, it is clear that in the preceding Office Action dated December 29, 2009, the Examiner understood that the claims required at least the three cell types (i.e., keratinocyte basal cells, melanocytes, and fibroblasts). Specifically, the Examiner cited Van Bossuyt to support the position that skin contains keratinocytes, melanocytes, and fibroblasts, and that Noel-Hudson's biopsy contains "all of the cell types recited in claims 29, 61, and 65." See Office Action dated December 29, 2009 at page 6. Therefore, the Examiner has previously considered as a claim limitation that the claimed composition includes keratinocyte basal cells, melanocytes, and fibroblasts (i.e., in the preceding Office Action dated December 29, 2009). Thus, this claim limitation cannot be reasonably said to be considered for the first time in the outstanding Office Action.

At least because the recitation of keratinocyte basal cells, melanocytes, and fibroblasts was not presented for the first time, Applicants respectfully submit that the new grounds of rejection made in the final Office Action are neither necessitated by a claim amendment nor an information disclosure statement. As such, the conditions set forth in MPEP § 706.07(a) have not been satisfied. Accordingly, Applicants respectfully request the finality of the final Office Action be reconsidered and withdrawn. Entry of the present Amendment and Response is also requested.

In the Claims

Claims 29, 61, 63, 65, and 75-79 were considered in the Office Action of July 9, 2010. Claims 34-60, 62, and 67-74 stand withdrawn from consideration. Claims 29, 61, 63, 65, and 75-79 stand rejected.

Applicants hereby amend claims 29 and 61 for clarity. Claim 29 has also been amended to correct typographical errors (i.e., to replace "μM" with "μm"). New claims 80-87 have been added. The amendments to claims 29 and 61 are supported by the originally filed claims and specification (e.g., page 7, line 10; page 21, line 11; page 22, line 11; page 5, lines 14-16; page 8, lines 20-21; and page 11, line 25). Support for new claims 80 and 83 can be found, for example, in the originally filed specification at page 22, lines 10-13. Support for new claims 81 and 85 can be found, for example, in the originally filed specification at page 11, lines 1-6. Support for new claims 82 and 86 can be found, for example, in the originally filed specification at page 8, lines 3-6 and page 12, lines 20-23. Support for new claims 83 and 87 can be found, for example, in the originally filed specification at page 12, lines 7-9 and page 4, lines 7-9. No new matter is introduced by these amendments.

Applicants have amended certain claims solely to expedite prosecution of the application. In making these amendments, Applicants are not acquiescing to the pending rejections and are not abandoning or surrendering any of the subject matter in previous versions or listings of the claims or in the application. Accordingly, Applicants reserve the right to pursue claims of similar, narrower, or broader scope in the future.

In view of the amendments to the claims and the following remarks, Applicants respectfully request reconsideration and withdrawal of all grounds of rejection.

Rejection Under 35 U.S.C. § 102(b)

Claims 29, 61, 63, and 75-79

Claims 29, 61, 63, and 75-79 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 97/23602 by Baur et al. ("Baur"). Applicants respectfully traverse this basis of rejection because Baur does not disclose every claimed element as amended.

Independent claims 29 and 61, as amended, recite that the cell suspension for immediate dispersion to the graft site includes viable keratinocyte basal cells, melanocytes and fibroblasts

harvested at the dermal-epidermal junction, and that the nutrient solution is suitable for direct application to the graft site. The Examiner noted on page 8 of the September 23, 2008 Final Office Action that "[l]imitations such as 'a cell suspension ... suitable for direct application to a region on a patient undergoing tissue grafting' are statements of intended use; see M.P.E.P. § 2111.02." Applicants respectfully submit that M.P.E.P. § 2111.02 concerns the effect of preamble and thus is not applicable to Applicants' claims as amended, because the amended claims recite structural or functional limitations such as "for immediate dispersion to the graft site," "harvested at the dermal-epidermal junction," and "suitable for direct application to the graft site."

It should also be noted that certain limitations provided in the amended claims, although may be functional in nature, such functional language does not render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). As clearly provided in M.P.E. P. § 2173.05(g), "[a] functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step."

Applicants respectfully submit that Baur does not anticipate claims 29 and 61 as amended because Baur does not disclose every claimed element. First, Baur does not disclose a cell suspension for immediate dispersion to the graft site that includes viable keratinocyte basal cells, melanocytes and fibroblasts. Instead, Baur discloses a cell culture for skin grafting that does not include fibroblasts. In particular, Baur produces "primary keratinocyte or melanocytes produced under serum free conditions without the use of any feeder cells, said primary keratinocytes and melanocytes being used for skin grafting." Baur at page 5, lines 13-15, emphasis added. Further, Baur provides that feeder cells include fibroblasts by stating " 'feeder cells' (e.g., fibroblasts)." See Baur at page 5, line 11. Thus, one of ordinary skill in the art would understand that Baur does not include fibroblasts in its cell culture for skin grafting.

The Examiner's position is that Baur teaches a cell suspension comprising melanocytes, keratinocytes, and fibroblasts. Office Action at page 2. However, Baur's cell suspension is not for immediate dispersion to the graft site. Rather, Baur obtains and prepares a skin sample "such that it is suitable for culturing in vitro." Baur at page 8, lines 18-19, emphasis added. The cells

from the skin sample are cultured and expanded, where "the expanded primary melanocytes or keratynocytes may be used prior to immortalization, e.g., in skin grafting." Baur at page 16, lines 6-7, emphasis added. Specifically, Baur provides that, "a cell suspension produced from skin samples described in example 1, which contains dissociated melanocytes, keratinocytes and fibroblasts, are cultured in the subject NR-3 medium." Baur at page 23, lines 19-21.

Second, Baur fails to disclose a cell suspension comprising cells harvested at the dermal-epidermal junction. Rather, Baur separates the dermis and epidermis, and prepares cells from the dermis and epidermis separately. Indeed, Baur from page 8, line 25 to page 9, line 2 and page 21, lines 21-27 provides:

> The resultant skin sections are then preferably separated into dermis and epidermis. This may be effected by physical and/or enzymatic means. For example, this may be effected by trypsinization, e.g. by floating skin sheets in a trypsin solution (e.g. about 0.5%) containing EDTA (e.g. about 0.1%) for a sufficient time to effect cell separation, e.g. about 30-60 minutes at 37°C or overnight at 4°C.
>
> The dermis is separated (to isolate the fibroblasts, see EXAMPLE 2) and the epidermis is then placed in a suspension medium. Preferably the suspension medium will contain soybean trypsin inhibitor solution (SBTI) and will be contacted with the cells for a sufficient time, typically about 5 minutes, in order to inactivate the trypsin and provide for cell release. Tissue culture medium will then be added, preferably serum-free NR-2 medium (described infra) and a filter (e.g. 100 mm filter) to obtain the desired cells, i.e. keratinocytes and/or melanocytes.
>
> Human fibroblasts were isolated from the skin samples FKO-NR, GKO- NR, DKO-NR. After the separation of the dermal and epidermal compartment the dermis was cut into small pieces 0.2 x 0.2 mm and fixed on a 6cm culture plate with serum. Dulbecco's minimal essential medium (DMEM, 10% FCS) was added after 2-4 hours. This explant culture was then incubated until fibroblast outgrowth was visible. Confluent fibroblast cultures were split and expanded for frozen stocks.

Thus, it is clear that Baur independently isolates cells from the entire dermal layer and from the entire epidermal layer, as opposed to the dermal-epidermal junction.

The Examiner took the position that the claims are product-by-process claims and "are not necessarily limited by the steps in the claims. See M.P.E.P § 2113." Office Action at page 3. However, M.P.E.P § 2113 also provides that "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the

product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding 'interbonded by interfusion' to limit structure of the claimed composite and noting that terms such as 'welded,' 'intermixed,' 'ground in place,' 'press fitted,' and 'etched' are capable of construction as structural limitations.)." Following the same line of reasoning, "harvested at the dermal-epidermal junction" is capable of construction as a structural limitation, because the process step (e.g., choice of the dermal-epidermal junction as the starting material) imparts distinctive structural characteristics to the final composition.

The Examiner also alleges that "Baur teaches a cell suspension… in a serum-free medium." Office Action at page 2. However, while Baur may produce melanocytes and keratinocytes in a serum-free medium, it does not produce fibroblasts under serum-free conditions. Rather, Baur prepares fibroblasts in the presence of serum. Specifically, Baur states that "[h]uman fibroblasts were isolated from the skin samples FKO-NR, GKO- NR, DKO-NR. After the separation of the dermal and epidermal compartment the dermis was cut into small pieces 0.2 x 0.2 mm and fixed on a 6cm culture plate with serum. Dulbecco's minimal essential medium (DMEM, 10% FCS) was added after 2-4 hours." Baur at page 21, lines 21-25, emphases added. In contrast, Applicants harvest cells in a nutrient solution that is free of serum xenogenic to the patient.

Third, Baur does not disclose a nutrient solution suitable for direct application to the graft site. Rather, Baur teaches tissue culture media for in vitro culturing. Baur at page 4, lines 31-33 and page 8, line 19. Baur is silent with regard to direct application of the tissue culture media to skin graft site.

For at least the foregoing reasons, claims 29 and 61 are patentable over Baur. Claims 63 and 75-79 are dependent upon claim 61, and thus are also patentable over Baur. Accordingly, Applicants respectfully request that the rejection of claims 29, 61, 63, and 75-79 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Claim 65

Claim 65 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Baur in view of U.S. Patent No. 6,432,666 to Hart ("Hart"). Applicants respectfully traverse this basis of rejection because Baur in view of Hart does not disclose every claimed element as amended.

Claim 65 depends upon claim 61. Claim 61 as amended is patentable over Baur for reasons discussed above. Hart does not remedy the deficiencies of Baur at least because Hart is cited solely as teaching that trypsinized skin suspensions contain Langerhans cells. See Office Action at page 3.

For at least the foregoing reasons, claim 61 and its dependent claim 65 are patentable over Baur in view of Hart. Accordingly, Applicants respectfully request that the rejection of claim 65 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 29, 61, 63, 65, and 75-79 stand rejected under 35 U.S.C. § 103(a) as allegedly being anticipated by Baur in view of U.S. Patent No. 5,328,695 to Lucas et al. ("Lucas") and Hart. Applicants respectfully traverse this basis of rejection because Baur in view of Lucas and Hart does not teach, suggest, or make obvious every claimed element as amended.

Independent claims 29 and 61, as amended, recite that the cell suspension for immediate dispersion to the graft site includes viable keratinocyte basal cells, melanocytes and fibroblasts harvested at the dermal-epidermal junction, and that the nutrient solution is suitable for direct application to the graft site. Baur, Lucas, and Hart do not teach or suggest these elements, nor would it have been obvious to one of ordinary skill in the art to modify the cited art to produce claims 29 and 61.

As discussed above, Baur does not teach or suggest a cell suspension for immediate dispersion to the graft site that includes viable keratinocyte basal cells, melanocytes and fibroblasts. Instead, Baur prepares cells "without 'feeder cells' (e.g., fibroblasts)" and thus teaches excluding fibroblasts. Baur, *supra*. Furthermore, Baur's mere mentioning of skin grafting relates only to keratinocytes and melanocytes and excludes fibroblasts. Baur, *supra*. In addition, Baur teaches in vitro culturing of keratinocytes and melanocytes prior to skin grafting. Baur, *supra*. As such, Baur explicitly teaches away from Applicants' claimed cell suspension that is for immediate dispersion.

Baur also fails to teach or suggest a cell suspension harvested at the dermal-epidermal junction. Rather, Baur harvests cells from separated dermis and epidermis separately and independently. Baur, *supra*. Baur uses the entire dermis and epidermis, as opposed to specific

compartment of the skin (i.e., the dermal-epidermal junction as Applicants' claims require). Baur, *supra*. Even if Baur may independently harvest different cell types, and then combine the cells in one suspension, the resulting cell composition would still be inherently distinct from those harvested at the dermal-epidermal junction. Indeed, one of ordinary skill in the art would understand that such contrasting methods necessarily result in distinctive structural characteristics to the final cell composition.

Baur's cell culture is inherently distinct from Applicants' claimed cell suspension for the additional reason that Baur offers the opposite, incompatible teaching regarding cell harvesting methods. Baur provides different methods for dermal and epidermal cell isolation. In particular, Baur teaches that melanocytes and keratinocytes are produced in a serum-free medium, while fibroblasts are prepared in the presence of serum. Baur, *supra*. By contrast, Applicants' claimed cell suspension includes cells (including keratinocyte basal cells, melanocytes and fibroblasts) that are harvested in a nutrient solution that is free of serum xenogenic to the patient.

Furthermore, Baur does not teach or suggest a nutrient solution suitable for direct application to the graft site. Rather, Baur's media are for in vitro culturing. Baur, *supra*. One of ordinary skill in the art would understand that culture media generally include macronutrients, micronutrients, vitamins, amino acids or other nitrogen supplements, sugar, solidifying agents or support systems, and growth regulators. Indeed, Baur at pages 32-34 provides a list of ingredients that are rich in amino acids, vitamins, and other organic supplements. Because culture media are rich in nutrients, they are generally handled with care in highly sterile environments (e.g., in a sterile hood) to avoid microbial contamination. Given that Baur's culture media are rich in nutrients and susceptible to pathogen contamination, one of ordinary skill in the art would not consider them suitable for direct application to a graft site.

Lucas and Hart do not cure the deficiencies of Baur. Rather, Lucas is cited solely as teaching filtering cell suspensions and Hart is cited solely as teaching that trypsinized skin suspensions contain Langerhans cells. See Office Action at page 5. Thus, the combination of the references still fails to teach, suggest, or make obvious claims 29 and 61, as well as their dependent claims.

For at least the foregoing reasons, claims 29 and 61 are patentable over Baur in view of Lucas and Hart. Claims 63, 65, and 75-79 are dependent upon claim 61, and thus are also

patentable. Accordingly, Applicants respectfully request that the rejection of claims 29, 61, 63, 65, and 75-79 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the claims, as amended, are in condition for allowance and request early favorable action. If the Examiner believes a telephonic interview would expedite the prosecution of the present application, the Examiner is welcome to contact Applicants' Attorney at the number below.

Respectfully submitted,

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